An exemplar population-based study to predict up-take of non-intensive therapies in acute myeloid leukaemia

Ip, Keith; Bedair, Khaled; Tauro, Sudhir

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1. Introduction

Recent advances in non-intensive therapy (non-IC) have demonstrated the potential for improved outcomes in patients with non-promyelocytic acute myeloid leukaemia (AML) unsuitable for intensive chemotherapy [1]. These data are mainly derived from clinical trial participants and therefore numbers of unselected patients that could benefit from novel agents are unknown. Identifying factors that influence treatment decisions in unselected patients would be useful to predict up-take of non-IC. A previous study on Medicare beneficiaries has identified variables influencing intensive treatment in older AML patients, but not the reasons for favouring SC over non-IC [2]. As the use of non-IC in patients increases [3], predicting the size of the target population for non-IC, identifying barriers to therapy and the determinants of survival in 'real-world' patients will help budgetary planning and patient outcomes. In the absence of a national registry of AML patients in the United Kingdom, through this retrospective study, we aimed to identify the proportion of AML patients that receives non-IC in our catchment population of 450,000, and factors affecting treatment and survival.

2. Methods

2.1. Study design and patient cohort

Following National Health Service (NHS) Caldicott Guardian approval, patients diagnosed with AML from 2001 to 2018 were identified from the data archives of the immunophenotyping laboratory. All patients were diagnosed and managed by haematologists based in NHS Tayside teaching hospitals. Medical and laboratory records were used to abstract information on age, gender, date of diagnosis, socio-economic status (SES), white cell count (WCC), cytogenetics, co-morbidity [4], distance from hospital (in miles), type of non-IC, or reasons for not receiving therapy, haematological improvement (HI, defined by transfusion-independence, absolute neutrophil count of ≥ 1 and unsupported platelet count ≥ 50) and date of death or last follow-up. The patient's residence postcode was used to infer SES, using the Scottish Index of Multiple Deprivation (SIMD) tool (https://www2.gov.scot/Topics/Statistics/SIMD) [5]. SIMD, a relative measure of deprivation, uses 7 domains (income, employment, education, health, access to services, crime and housing) to numerically rank different geographical areas. Indices were assigned to decile categorical indicators for SES, ranging from SES1 (lowest) to SES10 (highest).

2.2. End-points and statistical analysis

Determinants of treatment and overall survival (OS) were the study end-points. OS from the date of diagnosis to death or last follow-up was analysed using the log-rank test for Kaplan Meier survival. Co-variates potentially affecting treatment-decisions or OS (age, SES, co-morbidity, year of diagnosis, hospital-distance and WCC) were treated as continuous variables and analysed using the ANOVA or Mann-Whitney *U*. test Gender, karyotype (adverse or standard), non-IC and HI were considered as categorical co-variates for analysis using the Chi-Squared (χ^2) or Fisher's exact test (https://www.r-project.org/). All *P*-values were two-tailed and statistical significance was set at the level of $P < 0{\cdot}05$.

3. Results

3.1. Patient demographics and treatment determinants

Between 2001 and 2018, of 230 patients with an immunophenotypic diagnosis of AML, 121 were considered unsuitable for intensive chemotherapy and potentially eligible for non-IC. One patient who received azacitidine was excluded; of the remaining 120 patients (median age 77 years, range 44–91, 76 males and 44 females), 28 (23 %) received low-dose cyatarbine (40 mg per day subcutaneously for 10 days at intervals of 4–6 weeks) as a single agent, or in combination with other agents. Of the 92 patients managed exclusively with SC, reasons for not administering non-IC had been documented in 70 patients and included patient refusal (n = 10), perceived frailty (n = 30), including cognitive impairment (n = 2) and concurrent malignancy (n = 3), death before discussions (n = 3), secondary AML (n = 7) or adverse karyotype (n = 31). Multiple factors influenced the decision to not offer non-IC in 10 patients. The likelihood of receiving non-IC reduced with increasing co-morbidity (ANOVA F = 6.4, p = 0.013), adverse karyotype (χ^2 = 13, p < 0.001) and lower SES (ANOVA F = 4.1, p = 0.044) (Table 1). In total, 28 patients received non-IC (median 3 cycles, range 1–11).

3.2. Early mortality and disease response

Of 120 patients, 37 (31 %) died within 30 days of diagnosis; 18 (15 %) had survived for ≤ 10 days. In patients receiving non-IC, the 30-day mortality was lower (10 %) and comparable to clinical trials of non-IC that predominantly include [6] or restrict entry to patients with a performance status (PS) of ≤ 2 [7]. Disease response (HI) was observed in 5 (18 %) patients receiving non-IC.

3.3. Survival and determinants

The median survival for the entire cohort was 55 days (95 %CI 37–73), with survival in those receiving non-IC being superior (117 days, 95 %CI 70–164) to SC (46 days, 95 %CI 29–63, p = 0.031) (Fig. 1A). By univariate analysis, increasing age (HR 1.03 95 % CI

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Table 1
Variables influencing non-intensive therapy (non-IC).

Covariate	Total No. (%)	No. receiving non-IC (%)	p
Age			0.13
Median (range) 77 (44–91)			
≤70 years	34 (28)	8 (24)	
> 70 years	86 (72)	20 (23)	
Gender			0.82
Male	76	17 (22)	
Female	44	10 (23)	
SES (decile)			0.044
Median (range) 7 (1–10)			
1-3	28 (23)	9 (32)	
4–6	31 (26)	11 (35)	
7-10	61 (51)	8 (13)	
Year of diagnosis			0.56
≤2007	53 (44)	11 (21)	
> 2007	67 (56)	17 (23)	
White cell count (x 10^9/L)*			0.24
Median (range) 9 (0.6-303)			
≤10	60 (52)	16 (27)	
10-50	29 (25)	4 (14)	
≥50	26 (23)	8 (31)	
Cytogenetics*			0.001
Adverse	31 (26)	0 (0)	
Standard	87 (74)	28 (32)	
Charlson co-morbidity score*			0.013
Median (range) 6 (3–12)			
< 5	16 (14)	3 (19)	
≥5	99 (86)	24 (24)	
Hospital-distance			0.68
Median (range) 7.5 (1–51)			
< 5 miles	45 (38)	11 (24)	
5–10 miles	24 (20)	5 (21)	
> 10 miles	51 (41)	12 (24)	
Non-IC			
Yes		28 (23)	
No		92 (77)	

* data not available for all patients.

1.00–1.05, p = 0.045) and WCC (HR 1.01, 95 % CI 1.0–1.02, p = 0.000) associated with poorer survival. Survival improved with non-IC (HR 0.62, 95 % CI 0.40-0.96, p = 0.031) and HI (HR 0.36, 95 % CI 0.13-0.98, p = 0.045, n = 5). A favourable trend was also observed with higher SES (HR 0.94, 95 % CI 0.88–1.01, p = 0.074) and its associated variable, longer hospital-distance (HR 0.98, 95 %CI 0.97–1.0, p = 0.069) (p = 0.013, Pearson's correlation). No significant relationships between SES and WCC, or WCC and non-IC were identified.

When the survival of non-IC-treated patients without HI (non-responders, n = 23) was compared to SC (n = 92), the negative impact of a high WCC (HR 1.01, 95 % CI 1.00–1.02, p = 0.000) and benefits of higher SES (HR 0.91 95 % CI 0.85-0.98, p = 0.01) and longer hospital-distance (HR 0.98 95 %CI 0.97–1.00, p = 0.058) persisted but the OS benefit with non-IC was lost (HR 0.72, 95 % CI 0.45–1.15, p = 0.17) (Fig. 1B). In landmark analysis, a higher proportion of non-responders was alive at 90 days than SC (HR 2.13 95 %CI 1.09–4.15, p = 0.027) (Fig. 1B). No survival difference was observed at 180 days.

In analysis adjusted for hospital-distance, WCC and non-IC, SES was the only co-variate associating with survival (HR 0.91, 95 % CI 0.84-0.98, p = 0.015) for the entire cohort and non-responders (HR 0.89, 95 % CI 0.82-0.97, p = 0.005) including at 90 days (HR 0.90, 95 % CI 0.82-0.99, p = 0.028). The association between improved survival and SES has been suggested in a UK-based General Practice dataset, although patients were not stratified by treatment-intensity [8].

4. Discussion

Based on our experience in a single-payer health system, < 50 % of AML patients unsuitable for intensive chemotherapy will be candidates for novel non-IC. This figure could be lower, as our methodology for identifying AML patients may have excluded untreated patients in whom immunophenotyping was not undertaken to confirm AML. Since our patient cohort consisted exclusively of those treated with low-dose cytarabine, target numbers for non-IC could increase with the availability of more potent anti-leukemic drugs, particularly in disease with poor-risk genetic features. However, non-biological factors [9] including SES and immortal time bias (often unrepresented in clinical trials) are likely to remain important determinants of treatment. To optimize up-take of non-IC, the reasons for lower SES patients being less likely to receive treatment require study, and using objective measures of frailty should aid unbiased decision-making.

Amongst determinants of survival, the negative impact of socio-economic deprivation independent of non-IC and HI, was of particular interest in the absence of a correlation between SES and co-morbidity. Plausible biological reasons include greater frailty in patients from lower SES or differences in the delivery of supportive care including anti-microbial prophylaxis, but non-biological factors such as lower levels of motivation, compliance and/or early engagement with healthcare professionals too may contribute to inferior survival in those with lower SES, as suggested in the setting of intensive chemotherapy [10].

While advances in non-IC will improve outcomes in a proportion of AML patients, and broadening eligibility criteria in clinical trials may make the results more realistic, a holistic approach aiming to understand and improve patient perceptions and experience, particularly in relation to SES is essential to reduce unconscious bias and offer equitable healthcare.

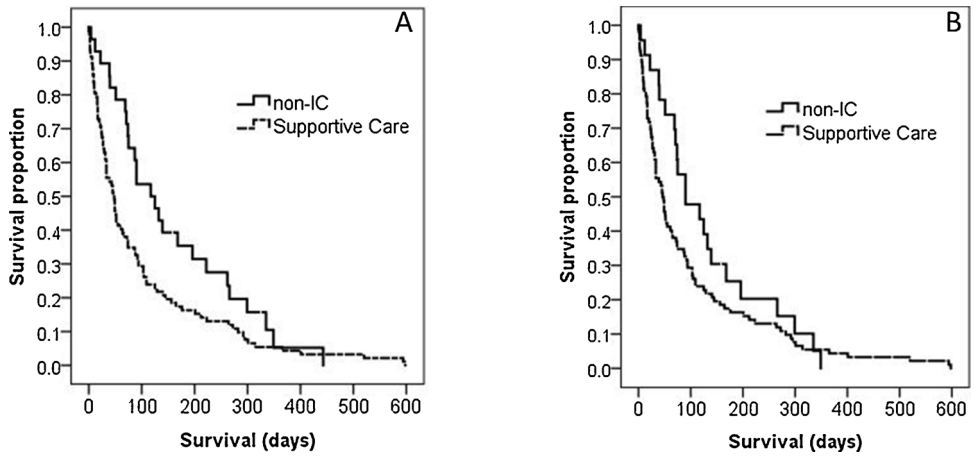

Fig. 1. Overall survival (OS) of AML patients unsuitable for intensive chemotherapy. Patients receiving non-IC had a superior survival compared to those receiving Supportive Care (A). Despite absence of HI, more patients receiving non-IC were alive at 90 days than those on Supportive Care (B).

Contributions

KI undertook data collection, KB performed statistical analysis and ST developed the study concept, helped with data collection and analysis and wrote the manuscript.

Declaration of Competing Interest

None.

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Keith Ip
Dundee Cancer Centre, School of Medicine, Ninewells Hospital, Dundee, DD1 9SY, Scotland, United Kingdom

Khaled Bedair[a,b]
[a] *Photobiology Unit, Dermatology Department, School of Medicine, University of Dundee, Dundee, DD1 9SY, UK*
[b] *Department of Statistics and Mathematics, Faculty of Commerce, Tanta University, Tanta, 31521, Egypt*

Sudhir Tauro*
Dundee Cancer Centre, School of Medicine, Ninewells Hospital, Dundee, DD1 9SY, Scotland, United Kingdom
E-mail address: s.tauro@dundee.ac.uk.

* Corresponding author at: Department of Haematology, Ninewells Hospital & Medical School, University of Dundee, Dundee, DD1 9SY, United Kingdom.